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Stephen Hordley

Dated

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Patent reference T1642PV

Patent application number 0326633.5
The Patent Office will fill in this part) 14 NOV 2003

Name, address and postcode of the applicant (underline all surnames)
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Patents ADP number (if you know it) 00597799001 ✓

If the applicant is a corporate body, give the country/state of its incorporation United Kingdom

Title of the invention Therapeutic agents

Name of your agent (if you have one) Mr. J. Horgan

Address for service" in the United Kingdom which all correspondence should be sent including the postcode)
Merck & Co., Inc.
European Patent Department
Terlings Park
Eastwick Road
Harlow
Essex CM20 2QR

Patents ADP number (if you know it) 07536832001 ✓

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Country	Priority Application number (if you know it)	Date of filing (day/month/year)
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Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if: Yes

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Patents Form 1/77

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11.

I/We request the grant of a patent on the basis of this application.

Signature

Mr. J. Horgan

Date 14 November 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. J. Horgan

01279 440625

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THERAPEUTIC AGENTS

The present invention is concerned with 1,2-dihydro-2-(*para*-substituted aryl/heteroaryl)-5 or 6-aryl/heteroaryl-3H-indazol-3-ones and analogues and derivatives thereof as well as pharmaceutically acceptable salts and prodrugs thereof, which are useful as therapeutic compounds, particularly in the treatment of pain and other conditions ameliorated by the modulation of the function of the vanilloid¹ receptor (VR1).

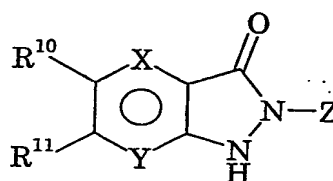
The pharmacologically active ingredient of chilli peppers has been recognised for some time to be the phenolic amide capsaicin. The application of capsaicin to mucous membranes or when injected intradermally, causes intense burning-like pain in humans. The beneficial effects of topical administration of capsaicin as an analgesic is also well established. However, understanding of the underlying molecular pharmacology mediating these responses to capsaicin has been a more recent development.

The receptor for capsaicin, termed the vanilloid VR1 receptor, was cloned by Caterina and colleagues at UCSF in 1997 (*Nature*, 398:816, 1997). VR1 receptors are cation channels that are found on sensory nerves that innervate the skin, viscera, peripheral tissues and spinal cord. Activation of VR1 elicits action potentials in sensory fibres that ultimately generate the sensation of pain. Importantly the VR1 receptor is activated not only by capsaicin but also by acidic pH and by noxious heat stimuli. It is also sensitized by a number of inflammatory mediators and thus appears to be a polymodal integrator of painful stimuli.

The prototypical VR1 antagonist is capsazepine (Walpole *et al.*, *J. Med. Chem.*, 37:1942, 1994) – VR1 IC₅₀ of 420nM. A novel series of sub-micromolar antagonists has also been reported recently (Lee *et al.*, *Bioorg. Med. Chem.*, 9:1713, 2001), but these reports provide no evidence for *in vivo* efficacy. A much higher affinity antagonist has been derived from the 'ultra-potent' agonist resiniferatoxin. Iodo-resiniferatoxin (Wahl *et al.*, *Mol. Pharmacol.*, 59:9, 2001) is a nanomolar antagonist of VR1 but does not possess properties suitable for an oral pharmaceutical. This last is also true of the micromolar peptoid antagonists described by Garcia-Martinez (*Proc. Natl. Acad. Sci., USA*, 99:2374, 2002). Most recently International (PCT) patent

publication No. WO 02/08221 has described a novel series of VR1 antagonists, which are stated to show efficacy in a number of animal models. We herein describe another novel series of VR1 modulators. These comprise predominantly VR1 antagonists but encompass VR1 partial antagonists and VR1 partial
5 agonists. Such compounds have been shown to be efficacious in animal models of pain.

The present invention provides compounds of formula (I):



(I)

10

wherein X and Y are each CR¹ or N;

one of R¹⁰ and R¹¹ is R¹ and the other is W;

each R¹ is hydrogen, halogen, hydroxy, cyano, amino, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl or haloC₁₋₄alkoxy;

15

W is a phenyl ring or a six-membered heteroaromatic ring containing one, two or three nitrogen atoms, which ring is optionally substituted by halogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cyano, nitro, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, haloC₁₋₆alkyl, haloC₁₋₆alkoxy, carboxy, hydroxyC₁₋₆alkyl or aminoC₁₋₆alkyl; and

20

Z is a phenyl ring or a six-membered heteroaromatic ring containing one, two or three nitrogen atoms, which ring is substituted at least at the position *para* to the attachment of the ring to the rest of the molecule by halogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cyano, nitro, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, haloC₁₋₆alkyl, haloC₁₋₆alkoxy, carboxy, hydroxyC₁₋₆alkyl or
25 aminoC₁₋₆alkyl;

or a pharmaceutically acceptable salt thereof.

R¹ is preferably hydrogen, halogen, hydroxy, cyano, amino, C₁₋₂alkyl, C₁₋₂alkoxy, haloC₁₋₂alkyl or haloC₁₋₂alkoxy, R¹ is more preferably fluorine, methyl or hydrogen. R¹ is generally hydrogen.

X and Y are generally CR¹.

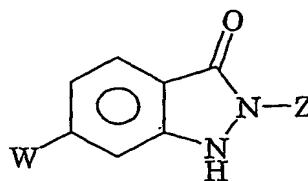
W is preferably unsubstituted or substituted by one, two or three substituents independently chosen from halogen, C₁₋₂alkyl, C₁₋₂alkoxy, cyano, nitro, amino, C₁₋₂alkylamino, di(C₁₋₂alkyl)amino, haloC₁₋₂alkyl, haloC₁₋₂alkoxy, hydroxyC₁₋₂alkyl or aminoC₁₋₂alkyl. More preferably W is optionally substituted by hydrogen, C₁₋₂alkyl, C₁₋₂alkoxy, haloC₁₋₂alkyl or haloC₁₋₂alkoxy. Most preferably the optional substituent is trifluoromethyl, methyl or methoxy. W is preferably monosubstituted. W preferably possesses a substituent at the position *ortho* to the point of attachment to the rest of the molecule. W is most preferably monosubstituted at the position *ortho* to the point of attachment to the rest of the molecule.

W is preferably a phenyl or pyridyl ring. Particular embodiments of W are 3-trifluoromethylpyrid-2-yl, 3-methylpyrid-2-yl and 2-methoxyphenyl.

Z is preferably substituted by one or two substituents independently chosen from halogen, C₁₋₂alkyl, C₁₋₂alkoxy, cyano, nitro, amino, C₁₋₂alkylamino, di(C₁₋₂alkyl)amino, haloC₁₋₂alkyl, haloC₁₋₂alkoxy, hydroxyC₁₋₂alkyl and aminoC₁₋₂alkyl. More preferably Z is substituted by halogen, methyl, trifluoromethyl, methoxy or trifluoromethoxy. Most preferably Z is substituted by trifluoromethyl. Z may be monosubstituted. Z may be monosubstituted by trifluoromethyl. Z is preferably a substituted phenyl or pyridyl, especially a substituted phenyl. An embodiment of Z is 4-trifluoromethylphenyl.

Preferably R¹⁰ is R¹ and R¹¹ is W.

A subset of compounds of the present invention is represented by formula IA:



(IA)

in which W is phenyl or pyridyl optionally substituted by halogen, C₁₋₂alkyl, C₁₋₂alkoxy, haloC₁₋₂alkyl or haloC₁₋₂alkoxy; and

Z is phenyl or pyridyl substituted at the position *para* to the point of attachment to the rest of the molecule by halogen, C₁₋₂alkyl, C₁₋₂alkoxy, haloC₁₋₂alkyl or haloC₁₋₂alkoxy;

or a pharmaceutically acceptable salt thereof.

5 W is preferably substituted at a position *ortho* to the point of attachment to the rest of the molecule. W is preferably monosubstituted. The substituent on W is preferably trifluoromethyl, methyl, trifluoromethoxy or methoxy. W is most preferably methyl, trifluoromethyl or methoxy.

10 Z is preferably substituted by fluorine, methyl, methoxy, trifluoromethyl or trifluoromethoxy. Z is preferably trifluoromethyl. Z is preferably a substituted phenyl.

Particular embodiments of the invention include:

1,2-dihydro-2-(4-trifluoromethylphenyl)-6-(3-trifluoromethyl-2-pyridinyl)-3H-indazol-3-one;

15 1,2-dihydro-6-(3-methyl-2-pyridinyl)-2-(4-trifluoromethylphenyl)-3H-indazol-3-one;

1,2-dihydro-2-(4-trifluoromethylphenyl)-5-(3-trifluoromethyl-2-pyridinyl)-3H-indazol-3-one;

1,2-dihydro-6-(2-methoxyphenyl)-2-(4-trifluoromethylphenyl)-3H-indazol-3-one;

20 and

1,2-dihydro-6-(3-methyl-2-pyridinyl)-2-(4-trifluoromethylphenyl)-3H-pyrazolo [3,4-b]pyridin-3-one;

or a pharmaceutically acceptable salt thereof.

25 As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

30 As used herein, the term "hydroxC₁₋₆alkyl" means a C₁₋₆alkyl group in which one or more (in particular 1 to 3, and especially 1) hydrogen atoms have been replaced by hydroxy groups. Particularly preferred are hydroxC₁₋₃alkyl groups, for example, CH₂OH, CH₂CH₂OH, CH(CH₃)OH or C(CH₃)₂OH, and most especially CH₂OH. "Aminoalkyl" shall be construed in an analogous manner.

As used herein, the terms "haloC₁₋₆alkyl" and "haloC₁₋₆alkoxy" means a C₁₋₆alkyl or C₁₋₆alkoxy group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by halogen atoms, especially fluorine or chlorine atoms. Preferred are fluoroC₁₋₆alkyl and fluoroC₁₋₆alkoxy groups, in particular, fluoroC₁₋₃alkyl and fluoroC₁₋₃alkoxy groups, for example, CF₃, CH₂CH₂F, CH₂CHF₂, CH₂CF₃, OCF₃, OCH₂CH₂F, OCH₂CHF₂ or OCH₂CF₃, and most especially CF₃ and OCF₃.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part of a group means that the group is straight or branched. Examples of suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is acetylene or propargyl.

When used herein, the term "halogen" means fluorine, chlorine, bromine and iodine. The most preferred halogens are fluorine and chlorine, especially fluorine.

Examples of 6-membered heterocycles are pyridine, pyrimidine, pyrazine, pyridazine and triazine.

In a further aspect of the present invention, the compounds of formula I may be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g.

sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

5 The salts may be formed by conventional means, such as by reacting the free base form of the compound of formula I with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

10 The present invention also includes within its scope N-oxides of the compounds of formula I above. In general, such N-oxides may be formed on any available nitrogen atom. The N-oxides may be formed by conventional means, such as reacting the compound of formula I with oxone in the presence of wet alumina.

15 The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

20 A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as
25 chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

The present invention includes within its scope solvates of the compounds of formula I and salts thereof, for example, hydrates.

30 The compounds according to the invention may have one or more asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, the compounds of formula I may also exist in tautomeric forms and the invention includes within its scope both mixtures and separate individual tautomers.

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula I in association with a pharmaceutically acceptable carrier or excipient.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices, suppositories, creams or gels; for oral, parenteral, intrathecal, intranasal, sublingual, rectal or topical administration, or for administration by inhalation or insufflation. Oral compositions such as tablets, pills, capsules or wafers are particularly preferred. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid pre-formulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these pre-formulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid pre-formulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Favoured unit dosage forms contain from 1 to 500 mg, for example 1, 5, 10, 25, 50, 100, 300 or 500 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or
5 suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of painful conditions such as those listed below, a
10 suitable dosage level is about 1.0 mg to 15 g per day, preferably about 5.0 mg to 1 g per day, more preferably about 5 mg to 500 mg per day, especially 10 mg to 100 mg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

It will be appreciated that the amount of a compound of formula I required
15 for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

The invention further provides a compound of formula I as defined above,
20 or a pharmaceutically acceptable salt thereof, for use in treatment of the human or animal body. Preferably, said treatment is for a condition which is susceptible to treatment by modulation (preferably antagonism) of VR1 receptors.

The compounds of the present invention will be of use in the prevention or
treatment of diseases and conditions in which pain and/or inflammation
25 predominates, including chronic and acute pain conditions. Such conditions include rheumatoid arthritis; osteoarthritis; post-surgical pain; musculo-skeletal pain, particularly after trauma; spinal pain; myofascial pain syndromes; headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain; ear pain;
30 episiotomy pain; burns, and especially primary hyperalgesia associated therewith; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for example, dysmenorrhoea, pain associated with cystitis and labour pain, chronic pelvic pain, chronic prostatitis and endometriosis; pain associated with nerve and

root damage, such as pain associated with peripheral nerve disorders, for example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; itching conditions including pruritis, itch due to hemodialysis, and contact dermatitis; pain (as well as broncho-constriction and inflammation) due to exposure (e.g. via ingestion, inhalation, or eye contact) of mucous membranes to capsaicin and related irritants such as tear gas, hot peppers or pepper spray; neuropathic pain conditions such as diabetic neuropathy, chemotherapy-induced neuropathy and post-herpetic neuralgia; "non-painful" neuropathies; complex regional pain syndromes; pain associated with carcinoma, often referred to as cancer pain; central nervous system pain, such as pain due to spinal cord or brain stem damage, low back pain, sciatica and ankylosing spondylitis; gout; scar pain; irritable bowel syndrome; inflammatory bowel disease; urinary incontinence including bladder detrusor hyper-reflexia and bladder hypersensitivity; respiratory diseases including chronic obstructive pulmonary disease (COPD), chronic bronchitis, cystic fibrosis, asthma and rhinitis, including allergic rhinitis such as seasonal and perennial rhinitis, and non-allergic rhinitis; autoimmune diseases; and immunodeficiency disorders.

Thus, according to a further aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment or prevention of physiological disorders that may be ameliorated by modulating VR1 activity.

The present invention also provides a method for the treatment or prevention of physiological disorders that may be ameliorated by modulating VR1 activity, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

According to a further or alternative aspect, the present invention provides a compound of formula I for use in the manufacture of a medicament for the treatment or prevention of a disease or condition in which pain and/or inflammation predominates.

The present invention also provides a method for the treatment or prevention of a disease or condition in which pain and/or inflammation predominates, which method comprises administration to a patient in need

thereof of an effective amount of a compound of formula I or a composition comprising a compound of formula I.

According to a further aspect of the present invention, it may be desirable to treat any of the aforementioned conditions with a combination of a compound
5 according to the present invention and one or more other pharmacologically active agents suitable for the treatment of the specific condition. The compound of formula I and the other pharmacologically active agent(s) may be administered to a patient simultaneously, sequentially or in combination.

Thus, for example, for the treatment or prevention of pain and/or inflammation, a
10 compound of the present invention may be used in conjunction with other analgesics, such as acetaminophen (paracetamol), aspirin and other NSAIDs, including selective cyclooxygenase-2 (COX-2) inhibitors, as well as opioid analgesics, especially morphine, NR2B antagonists, bradykinin antagonists, anti-migraine agents, anticonvulsants such as oxcarbazepine and carbamazepine,
15 antidepressants (such as TCAs, SSRIs, SNRIs, substance P antagonists, etc.), spinal blocks, gabapentin, pregabalin and asthma treatments (such as β_2 -adrenergic receptor agonists or leukotriene D₄ antagonists (e.g. montelukast).

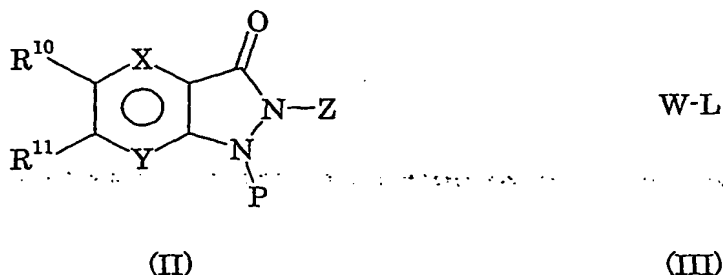
Specific anti-inflammatory agents include diclofenac, ibuprofen, indomethacin, nabumetone, ketoprofen, naproxen, piroxicam and sulindac,
20 etodolac, meloxicam, rofecoxib, celecoxib, etoricoxib, parecoxib, valdecoxib and tilcoxib. Suitable opioid analgesics of use in conjunction with a compound of the present invention include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone,
25 nalbuphine, propoxyphene and pentazocine; or a pharmaceutically acceptable salt thereof. Suitable anti-migraine agents of use in conjunction with a compound of the present invention include CGRP-antagonists, ergotamines or 5-HT₁ agonists, especially sumatriptan, naratriptan, zolmatriptan or rizatriptan.

Therefore, in a further aspect of the present invention, there is provided a
30 pharmaceutical composition comprising a compound of the present invention and an analgesic, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an

analgesic as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a disease or condition in which pain and/or inflammation predominates.

The compounds of formula I can be made by reacting a compound of
 5 formula II with a compound of formula III:

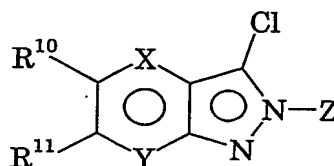


wherein W, X, Y and Z are as defined for formula I, P is hydrogen or a protecting
 10 group, one of R¹⁰ and R¹¹ is R¹ as defined above and the other is L¹ and one of L
 and L¹ is Cl or Sn(alkyl)₃, for example Sn(methyl)₃ or Sn(n-butyl)₃, and the other
 is bromine or chlorine, followed, if necessary, by deprotecting the compound
 obtained. When L or L¹ is Cl it can be initially converted into a group B(OH)₂
 under conditions suitable for a Suzuki Coupling Reaction (for review, see for
 15 instance A. Suzuki, *Pure Appl. Chem.*, 1991, 63, 419-422), for example, in the
 presence of a palladium catalyst such as
 tetrakis(triphenylphosphine)palladium(0),
 tris(dibenzylideneacetone)dipalladium(0),
 (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium or dichloro-(1,4-
 20 bis(diphenylphosphino)butane)palladium, in a suitable solvent such as an ether,
 for example, dimethoxyethane or dioxane or an aromatic hydrocarbon, for
 example toluene, at an elevated temperature and in the presence of a base such
 as sodium carbonate. Where L or L¹ is Sn(alkyl)₃, the reaction is conveniently
 effected under conditions suitable for a Stille Coupling Reaction (for review, see
 25 for instance J. K. Stille, *Angew. Chem. Int. Ed.*, 1986, 25, 508-524), for example,
 in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)
 palladium(0) or bis(triphenylphosphine)palladium(II) chloride, in a suitable
 solvent such as an ether, for example dioxane, or an aromatic hydrocarbon, for
 example, toluene, at an elevated temperature, and in the presence of catalysts

such as LiCl and CuI. The reaction can be carried out for from 10 to 15 minutes at from 150°C to 160°C in a microwave.

During the reaction a protecting group such as trimethylsilylethoxymethyl may be present. The group can be inserted by reacting with its chloride in the presence of a strong base such as sodium hydroxide in a solvent such as tetrahydrofuran at about room temperature under an inert atmosphere. It can be removed by heating to about reflux with an acid such as hydrochloric acid in a solvent such as ethanol generally for about one hour.

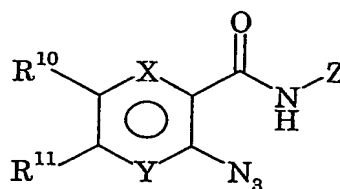
Compounds of formula II can be made by reacting a compound of formula IV:



(IV)

wherein X, Y and Z are as defined for formula I and R¹⁰ and R¹¹ are as defined above, with a base such as potassium hydroxide in a solvent such as methanol generally at a temperature of about 150°C in a microwave for about 15 minutes.

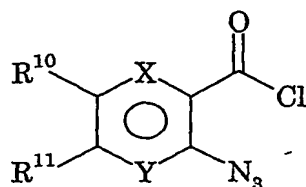
Compounds of formula IV can be made by reacting a compound of formula V:



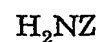
(V)

wherein X, Y and Z are as defined for formula I and R¹⁰ and R¹¹ are as defined above with a ring closing agent such as thionyl chloride generally at reflux for about 24 hours.

Compounds of formula V can be made by reacting a compound of formula VI with a compound of formula VII:



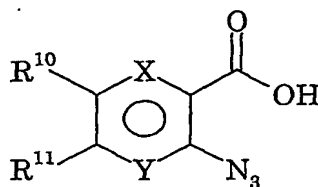
(VI)



(VII)

wherein X, Y and Z are as defined for formula I and R^{10} and R^{11} are as defined above generally in the presence of a catalyst such as 4-dimethylaminopyridine in a solvent such as dichloromethane at about room temperature for one hour.

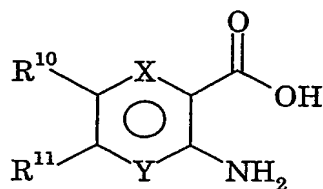
Compounds of formula VI can be made by reacting a compound of formula VIII:



(VIII)

wherein X and Y are as defined for formula I and R^{10} and R^{11} are as defined above, with a chlorinating agent such as thionyl chloride generally at reflux for about two hours.

Compounds of formula VIII can be made by reacting a compound of formula IX:



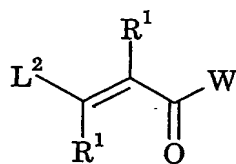
(IX)

wherein X and Y are as defined for formula I and R¹⁰ and R¹¹ are as defined above
 first with a mixture of an acid such as hydrochloric acid and a nitrite such as
 5 sodium nitrite generally in a solvent such as water at about 5°C and then with an
 azide such as sodium azide in the presence of a compound such as sodium acetate
 in a solvent such as water at about room temperature for about thirty minutes.

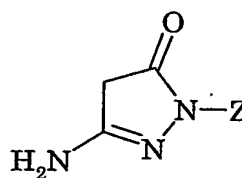
In an alternative process compounds of formula I can be made by reacting
 a compound of formula IV under conditions described above for a Suzuki or Stille
 10 coupling with a compound of formula III, followed by reaction with a base such as
 potassium hydroxide in a solvent such as methanol at about 160°C for about 2
 minutes in a microwave.

Compounds of formula I in which X is CR¹, Y is N, R¹⁰ is R¹ and R¹¹ is W
 can also be made by reacting a compound of formula X with a formula of XI:

15



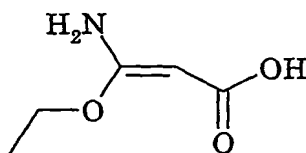
(X)



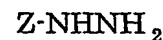
(XI)

in which R¹, W and Z are as defined for formula I and L² is a leaving group such
 as dimethylamino. The reaction is generally carried out in a solvent such as
 20 pyridine at about reflux for about three hours.

Compounds of formula XI can be made by reacting a compound of formula
 XII with a compound of formula XIII:



(XII)



(XIII)

in which Z is as defined for formula I generally in a solvent such as toluene at about reflux for about one hour.

5 Compounds of formula XII can be made from a preceding ester by reacting with a mild base such as potassium carbonate in a solvent such as ether at about 0°C.

Compounds of formula I can be converted to other compounds of formula I by standard methods.

10 Where the synthesis of intermediates and starting materials is not described these compounds are commercially available or known in the literature or can be made from commercially available compounds or compounds known in the literature by standard methods.

15 During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups
20 may be removed at a convenient subsequent stage using methods known from the art.

The following Examples serve to illustrate the preparation of compounds of the present invention.

25 Example 1 1,2-Dihydro-2-(4-trifluoromethylphenyl)-6-(3-trifluoromethyl-2-pyridinyl)-3H-indazol-3-one

Step 1: 2-Azido-4-bromobenzoic acid To a solution of 2-amino-4-bromobenzoic acid (8.4 g, 0.039 mol) in a mixture of concentrated HCl (70 mL) and H₂O

(100 mL) was added a solution of NaNO_2 (2.8 g, 0.044 mol) in H_2O (40 mL) such that the reaction temperature did not rise above 5°C . After addition was complete the resulting slurry was stirred for 15 min and the cold mixture added in aliquots to a solution of NaN_3 (2.5 g, 0.039 mol) and NaOAc (38 g, 0.47 mol) in H_2O (80 mL) at room temperature. The resulting slurry was stirred for 30 min and the solid collected by filtration giving 6.4 g (68% yield) of product as a tan powder. ^1H NMR (360 MHz, DMSO): 7.46 (1H, dd, J 1.4 and 7.5 Hz), 7.57 (1H, d, J 1.4 Hz), 7.70 (1H, d, J 7.5 Hz).

Step 2: 2-Azido-4-bromo-N-(4-trifluoromethylphenyl)-benzamide. The product of Step 1 (6.4 g, 0.026 mol) was heated in SOCl_2 (30 mL) at reflux for 2 h. The excess reagent was then evaporated and chased with toluene (2x10 mL). The residue was dissolved in dry CH_2Cl_2 (20 mL) and added dropwise to a solution of 4-(dimethylamino)pyridine (3.2 g, 0.026 mol) and 4-aminobenzotrifluoride (4.3 g, 0.026 mol) in CH_2Cl_2 (40 mL) cooled in ice. When addition was complete (10min), the mixture was stirred and warmed to room temperature over 1 h, then washed with 2N HCl (15 mL), 2N Na_2CO_3 solution (15 mL), brine (10 mL), dried (MgSO_4) and concentrated to give 8.4 g (84% yield) of product as a buff solid. ^1H NMR (360 MHz, CDCl_3): 7.40 (1H, d, J 1.4 Hz), 7.44 (1H, dd, J 1.4 and 8.5 Hz), 7.63 (2H, d, J 8.5 Hz), 7.80 (2H, d, J 8.5 Hz), 8.14 (1H, d, J 8.5 Hz).

Step 3: 6-Bromo-3-chloro-2-(4-trifluoromethylphenyl)-2H-indazole. A solution of the product of Step 2 (3g, 0.0078 mol) in SOCl_2 (15 mL) was heated at reflux for 24 h. The mixture was then concentrated and the residue partitioned between ether (3x20 mL) and Na_2CO_3 solution (10 mL). The organic phase was separated, dried (MgSO_4) and concentrated to give 2.5 g (85% yield) of product as a tan powder. ^1H NMR (360 MHz, CDCl_3): 7.25 (1H, d, J 8.9 Hz), 7.37 (1H, d, 8.9 Hz), 7.80-7.95 (5H, m).

Step 4: 1,2-Dihydro-6-bromo-2-(4-trifluoromethylphenyl)-3H-indazol-3-one. A solution of the product of Step 3 (2.4 g, 0.0064 mol) in 1M KOH in MeOH (16 mL) was heated at 150°C in a sealed tube via microwave irradiation for 15 min. The mixture was then concentrated, diluted with H_2O , acidified with 1N HCl and the resulting precipitate collected by filtration to give 1.0 g (44 % yield)

of product. ^1H NMR (360 MHz, CDCl_3): 7.37 (1H, dd, J 1.4 and 8.5 Hz), 7.66 (1H, d, 1.4 Hz), 7.73 (1H, d, 8.5 Hz), 7.89 (2H, d, 8.5 Hz), 8.13 (2H, d, 8.5 Hz), 11.0 (1H, s).

5 Step 5: 6-Bromo-1,2-dihydro-2-(4-trifluoromethylphenyl)-1-(2-trimethylsilyl
ethoxymethyl)-3H-indazol-3-one A suspension of NaH in mineral oil (60%, 0.17
 g, 0.0041 mol) was added portionwise to a solution of the product of Step 4 (1.3 g,
 0.0035 mol) in dry THF (50 mL) at room temperature under N_2 . After 20 min,
 SEM chloride (0.68 g, 0.0041 mol) in THF (15 mL) was added and the resulting
 10 slurry stirred at room temperature overnight. The mixture was quenched with
 brine (10 mL) and extracted into ether (3x20 mL). The organic phase was washed
 with 1N HCl (10 mL), 2N NaOH (10 mL), brine (10 mL), dried (MgSO_4) and
 concentrated to give crude product as an oil.

15 Step 6: 1,2-Dihydro-2-(4-trifluoromethylphenyl)-6-(3-trifluoromethyl-2-pyridinyl)-
1-(2-(trimethylsilyl)ethoxymethyl)-3H-indazol-3-one The product of Step 5 (1.3 g,
 2.6 mmol), was dissolved in dioxane (10 mL) and flushed with N_2 .
 Bis(pinacolato)diboron (680 mg, 2.6 mmol), bis(diphenylphosphino)ferrocenyl
 palladium(II) dichloride (60 mg) and KOAc (380 mg, 3.9 mmol) were added. The
 20 mixture was stirred at 100°C overnight. 2-Chloro-3-trifluoromethylpyridine
 (470 mg, 2.6 mmol), bis(diphenylphosphino)ferrocenyl palladium(II) dichloride
 (20 mg) and saturated Na_2CO_3 solution (1 mL) were added, and the mixture
 heated at reflux for a further 18 h. Purification by column chromatography gave
 0.2 g of product as an oil.

25 MS: (ES (M+1)) 554.

Step 7: 1,2-Dihydro-2-(4-trifluoromethylphenyl)-6-(3-trifluoromethyl-2-pyridinyl)-
3H-indazol-3-one The product of Step 6 (0.2 g), in a mixture of concentrated HCl
 (2 mL) and EtOH (3 mL), was heated at reflux for 1 h. The mixture was
 30 concentrated and the residue crystallized from EtOH/ H_2O to give 70 mg of
 product as a colourless solid. ^1H NMR (360 MHz, CDCl_3): 7.33 (1H, s), 7.39 (1H, d,
 J 8.0 Hz), 7.43 (1H, s), 7.5-7.55 (1H, m), 7.73 (2H, d, J 8.0 Hz), 7.99 (1H, d, J 8.0
 Hz), 8.09 (2H, d, J 8.0 Hz), 8.14 (1H, d, J 8.0 Hz), 8.9 (1H, d, J 8.0 Hz).

Example 2 1,2-Dihydro-6-(3-methyl-2-pyridinyl)-2-(4-trifluoromethylphenyl)-3H-indazol-3-one

The product of Example 1, Step 4 (0.35 g, 1 mmol), bis(diphenylphosphino)ferrocenyl palladium(II) dichloride 0 (40 mg), CuI (19 mg, 0.1 mmol), LiCl (126 mg, 3 mmol), 3-methyl-2-(tri-*n*-butylstannyl)pyridine (530 mg, 1.4 mmol) and dioxane (4 mL) were heated at 150°C for 15 min under microwave irradiation. The resulting mixture was purified by column chromatography (silica: EtAc:hexane 1:2->EtAc) to give 0.2 g (54%) of the title compound as a colourless solid. ¹H NMR (360 MHz, DMSO): 2.5 (3H, s), 7.30-7.40 (2H, m), 7.50 (1H, m), 7.78 (1H, d, *J* 7.7 Hz), 7.85 (1H, d, *J* 8.0 Hz), 7.90 (2H, d, *J* 8.5 Hz), 8.19 (2H, d, *J* 8.5 Hz), 8.53 (1H, d, *J* 4.6 Hz), 10.8 (1H, s).

Example 3 1,2-Dihydro-2-(4-trifluoromethylphenyl)-5-(3-trifluoromethyl-2-pyridinyl)-3H-indazol-3-one

This compound was prepared as described for Example 1 replacing 2-azido-4-bromobenzoic acid with 2-azido-5-bromobenzoic acid in Step 2. ¹H NMR (360 MHz, DMSO): 7.52 (1H, d, *J* 8.0 Hz), 7.65-7.75 (1H, m), 7.76 (1H, dd, *J* 1.2 and 8.0 Hz), 7.83 (1H, s), 7.91 (2H, d, *J* 8.0 Hz), 8.18 (2H, d, *J* 8.0 Hz), 8.34 (1H, d, *J* 8.0 Hz), 8.9 (1H, d, *J* 8.0 Hz), 11.1 (1H, s).

Example 4 1,2-Dihydro-6-(2-methoxyphenyl)-2-(4-trifluoromethylphenyl)-3H-indazol-3-one

Step 1: 3-chloro-6-(2-methoxyphenyl)-2-(4-trifluoromethylphenyl)-2H-indazole

A mixture of the product of Example 1 Step 3 (100 mg, 0.26 mmol), 2-methoxyphenylboronic acid (50 mg, 0.33 mmol), bis(diphenylphosphino)ferrocenyl palladium(II) dichloride 0 (20 mg), saturated Na₂CO₃ solution (1 mL) and dioxane (2 mL) was heated at 160°C for 10 min via microwave irradiation. The title product was then purified by preparative thin layer chromatography on silica eluting with EtAc:hexanes 1:5. MS: (ES (M+1)) 403, 405.

Step 2: 1,2-Dihydro-6-(2-methoxyphenyl)-2-(4-trifluoromethylphenyl)-3H-indazol-3-one

The product of Step 1 (100 mg) was dissolved in 1N KOH in MeOH (2 mL) and heated at 160°C for 2 min via microwave irradiation. The resulting yellow solution was concentrated, diluted with water and acidified with 2N HCl. The

precipitate was collected and recrystallised from EtOH/H₂O to give 21 mg of product as colourless needles. ¹H NMR (500 MHz, DMSO): 3.81 (3H, s), 7.08 (1H, t, *J* 7.4 Hz), 7.18 (1H, d *J* 7.4 Hz), 7.31 (1H, dd, *J* 1.2 and 8.0 Hz), 7.38 (1H, dd, *J* 1.2 and 8.0 Hz), 7.39-7.42 (1H, m), 7.44 (1H, s), 7.79 (1H, d, *J* 8.0 Hz), 7.89 (2H, d, *J* 8.5 Hz), 8.18 (2H, d, *J* 8.5 Hz), 10.76 (1H, s).

Example 5 1,2-Dihydro-6-(3-methyl-2-pyridinyl)-2-(4-trifluoromethylphenyl)-3H-pyrazolo[3,4-b]pyridin-3-one

Step 1: 5-Amino-2,4-dihydro-2-(4-trifluoromethylphenyl)-3H-pyrazol-3-one Ethyl 3-amino-3-ethoxy-2-propenoate hydrochloride (10g, 0.05 mol) was added to a mixture of 40% aqueous K₂CO₃ (70 mL) and ether (50 mL) cooled in ice. The organic phase was extracted with ether (2x50 mL) and the extracts dried (K₂CO₃) and concentrated to give 7 g of a gummy solid. A solution of 4-trifluoromethylphenylhydrazine (7.7 g, 0.043 mol) in toluene (50 mL) was added and the mixture heated at reflux for 1 h. The mixture was concentrated and the residue treated with a freshly prepared NaOEt in EtOH (Na (1.9 g, 0.082 mol), EtOH (50 mL)) and heated at reflux for 1 h. After concentration the residue was partitioned between ether (2x30 mL) and H₂O (50 mL). The aqueous phase was acidified and re-extracted with ether to give 6.0 g of product as an orange solid. ¹H NMR (360 MHz, CDCl₃): 3.5 (2H, s), 4.5 (2H, s), 7.60 (2H, d, *J* 8.5 Hz), 8.00 (2H, d, *J* 8.5 Hz).

Step 2: 1,2-Dihydro-6-(3-methyl-2-pyridinyl)-2-(4-trifluoromethylphenyl)-3H-pyrazolo[3,4-b]pyridin-3-one A mixture of the product of Step 1 (1.68 g, 0.0074 mol) and 3-(dimethylamino)-1-(3-methyl-2-pyridinyl)-2-propen-1-one (EP-A-0233461) (1.4 g, 0.0074 mol) in pyridine (20 mL) was heated at reflux for 3 h. The mixture was concentrated and then triturated to give a solid which was recrystallised from iPrOH to give 0.64 g (23% yield) of product as a yellow powder. ¹H NMR (360 MHz, DMSO): 2.6 (3H, s), 7.45-7.55 (1H, m), 7.55-7.65 (1H, m), 7.85-7.95 (3H, m), 8.20 (2H, d, *J* 8.5 Hz), 8.39 (1H, d, *J* 8.0 Hz), 8.61 (1H, d, *J* 4.6 Hz).

The above exemplified compounds of the present invention have been tested in the following assay and generally possess an $IC_{50} < 0.5 \mu M$ and, in the majority of cases, $< 200 \text{ nM}$.

5

Biological Methodology

Determination of *in vitro* activity

CHO cells, stably expressing recombinant human VR1 receptors and plated into black-sided 384-well plates, were washed twice with assay buffer (Hepes-buffered saline) and then incubated with $1 \mu M$ Fluo-3-AM for 60 minutes in darkness.

10 Cells were washed twice more to remove excess dye, before being placed, along with plates containing capsaicin and test compounds in a Molecular Devices FLIPR. The FLIPR simultaneously performed automated pharmacological additions and recorded fluorescence emission from Fluo-3. In all experiments, basal fluorescence was recorded, before addition of test compounds and

15 subsequent addition of a previously determined concentration of capsaicin that evoked 80% of the maximum response. Inhibition of capsaicin evoked increases in intracellular $[Ca^{2+}]$ were expressed relative to wells on the same plate to which capsaicin was added in the absence of test compounds. Increases in intracellular $[Ca^{2+}]$ occurring after addition of test compound alone, prior to addition of

20 capsaicin, allow determination of intrinsic agonist or partial agonist activity, if present.

25

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